38. (New) A method according to claim 16, wherein said effective endothelial-protecting amount of erythropoietin is administered after said chemotherapeutic agent.

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39. (New) The method of claim 16, wherein said chemotherapeutic agent is cisplatin.

Remarks

Applicants appreciate the thorough examination of the present application as evidenced by the Office Action dated January 21, 2003 (the Action). Claims 16-22 are pending in the present application. Claims 16-22 stand rejected. The concerns raised by the Examiner are addressed below as set forth in the Action.

I. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 16-22 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. More specifically, the Action asserts that with respect to claim 16 and dependent claims thereof, the recitation "mechanical damage" is unclear because a definition has not been provided in the specification. *See* Action, page 2-3. At page 3, the Action also asserts that the term "amount" cannot be determined because the intended "amount" is not defined in the specification. The Action further asserts that claims 16-22 are rejected as being incomplete for omitting essential steps that involve when and how to determine treatment of endothelial cell injury. *See* Action, page 3. Applicants respectfully traverse these rejections.

Applicants respectfully submit that the term "mechanical damage" as used in the specification is used in a manner consistent with the understanding of those of ordinary skill in the art. More specifically, the term "mechanical damage" is well-understood in the area of cardiovascular physiology as relating to damage of tissue resulting from exposure to mechanical, i.e., physical forces, as opposed to chemical or environmental forces. Well-known, non-limiting examples of mechanical damage include cutting, scraping, tearing, and stretching of the tissue. Thus, mechanical damage relates to the application of varying

degrees of force and/or pressure to the tissue. In view of the well-known definition and understanding of mechanical damage in the field of cardiovascular medicine and research, Applicants respectfully submit that the recitation "mechanical damage" does not render claim 16 and dependent claims thereof unclear.

Applicants have amended claim 16 to include the recitation "an effective endothelial-protecting amount of erythropoietin." Moreover, Applicants have added new claims 31-39 that include recitations related to the amount of erythropoietin to be administered to the subject. Support for the amendment to claim 16 and new added claims 30-39 can be found in the specification at page 12, line 6 through page 13, line 4, among other places. Applicants further note that one of ordinary skill in the art would be able to determine, by routine experimentation, the dosage of erythropoietin to achieve the desired effect. Thus, in view of the amendment of claim 16, the addition of new claims 31-39, and the disclosure in the specification providing dosage amounts for erythropoietin, Applicants respectfully submit that the metes and bounds of the term "amount" can be determined.

Applicants respectfully submit that claims 16-22 do not omit essential steps involving when and how to determine treatment of endothelial cell injury. Applicants note that amended claim 16 recites factors that can contribute to endothelial injury and provides for administration of an effective endothelial-protecting amount of erythropoietin to a subject in need of such treatment. Through routine experimentation, one of ordinary skill in the art can determine the dosage and timing of erythropoietin administration in order to achieve the desired effect.

Accordingly, Applicants respectfully submit that claims 16-22 are not indefinite under 35 U.S.C. § 112, second paragraph, and request that this rejection be withdrawn.

II. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 16-22 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. More specifically, the Action asserts that the specification "does not reasonably provide enablement for a method of treating endothelial cell injury, caused by mechanical damage, exposure to radiation, inflammation, heart disease, cancer, or other

chemotherapeutics." Action, page 3. The Action further asserts that "the specification has limited the instant invention to a method of protecting endothelial cells from cisplatin damage in vitro comprising the administration of EPO within the ranges 0.15-5U/ml, wherein the protective effect is interpreted as continued proliferation of endothelial cells in culture." Action, pages 5-6. Applicants respectfully traverse this rejection.

As noted in the Action on page 4, factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence of working examples, the breadth of the claims, and the quantity of experimentation needed. Applicants assert that evaluation of these factors in view of the present disclosure would lead one of ordinary skill in the art to conclude that the present application provides an enabling disclosure.

Turning specifically to the factor relating to the amount of direction or guidance present and the presence of working examples, Applicants note that one of ordinary skill in the art is apprised of the endothelial damage that occurs as a result of exposure to mechanical damage, exposure to radiation, exposure to chemotherapeutic agents, inflammation, heart disease, cancer, and other disease states known to damage the endothelium. Applicants provide in the specification, at page 5, line 33 through page 6, line 8, that administration of erythropoietin can provide protection against endothelial damage resulting from exposure to chemotherapeutic agents, radiation, mechanical trauma, and other disease states that damage the endothelium. Applicants present examples disclosed in the specification that relate to endothelial damage occurring as a result of exposure to chemotherapeutic agent, cisplatin. As noted in the *Manuel of Patent Examining Procedure* (M.P.E.P.), "[c]ompliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed." M.P.E.P. § 2164.02. Moreover, M.P.E.P. § 2164.02 further states that "because only an enabling disclosure is required, applicant need not describe all actual embodiments." Thus, where Applicants disclose a method of treating endothelial injury caused by mechanical damage, exposure to radiation, exposure to chemotherapeutic agents, inflammation, heart disease or cancer as recited in claim 1, Applicants submit that the present

application provides enablement for a method of treating endothelial cell injury resulting from the causes described therein.

With respect to Applicants presentation of *in vitro* data, Applicants submit that one of ordinary skill in the art is provided enough information in the form of *in vitro* data to determine an *in vivo* method of treating endothelial injury caused by mechanical damage, exposure to radiation, exposure to chemotherapeutic agents, inflammation, heart disease or cancer, in a subject, comprising administering an effective endothelial-protecting amount of erythropoietin to a subject in need of such treatment. Applicants note that the endothelial cell type and the nature of the experiments conducted are particularly suited for correlation of results obtained *in vitro* to results expected from *in vivo* experiments. Thus, the observed effects on the endothelial cells *in vitro* along with the dosage ranges as disclosed in the present specification at page 12, line 20 through page 13, line 4 provide one of ordinary skill in the art the tools to conduct routine experimentation to devise a treatment protocol for a subject in need of treatment as provided by the present application.

In view of the Applicants' disclosure provided in the present specification coupled with the knowledge of one of ordinary skill in the art concerning cardiovascular physiology, Applicants respectfully submit that the Examiner has not provided any reason to doubt the veracity of Applicants' statements. However, Applicants submit currently herewith a Declaration of Dr. George Sigounas under 37 C.F.R. § 1.132 (the Sigounas Declaration). The Sigounas Declaration presents supplemental information showing that erythropoietin effectively prevents or protects and/or repairs injuries of the endothelium caused by the chemotherapeutic agent bleomycin. Moreover, these studies are *in vivo* studies in an established mouse model. The *in vivo* studies suggest that erythropoietin is capable of protecting the endothelium from damage resulting thereto. The Sigounas Declaration merely confirms the enabling disclosure set forth in the specification as originally filed.

Accordingly, Applicants respectfully submit that claims 16-22 are enabled, and request that this rejection be withdrawn.

III. Claim Rejections Under 35 U.S.C. § 102

Claims 16 and 21 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Carline *et al.* Recombinant human erythropoietin stimulates angiogenesis *in vitro*. *Kidney Int.* **47(3)**: 740-5 (1995) (Carlini *et al.*). Applicants respectfully traverse this rejection.

"Anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention." *Apple Computer Inc. v. Articulate Systems Inc.* 57 USPQ2d 1057, 1061 (Fed. Cir. 2000) (*relying on Electro Med. Sys. S.A. v. Cooper Life Scis.*, 32 USPQ2d 1017, 1019 (Fed Cir. 1994).

The present invention is directed to a method of treating endothelial injury caused by mechanical damage, exposure to radiation, exposure to chemotherapeutic agents, inflammation, heart disease or cancer, in a subject, comprising administering an effective endothelial-protecting amount of erythropoietin to a subject in need of such treatment as recited in claim 16.

In contrast, Carlini *et al.* conducted *in vitro* studies to address the question of whether recombinant human erythropoietin stimulates angiogenesis. These authors conclude that their data suggest recombinant human erythropoietin could have "a deleterious effect on the vascular endothelium, inducing angiogenesis and increasing ET-1 [endothelin-1] which is involved in atherosclerosis, hypertension and vascular restenosis." *See* page 744. The beneficial angiogenic use of recombinant human erythropoietin proposed by these authors is the possible induction of neovascularization in hypovascular tissues. *See* page 744. Carlini *et al.* do not predict that the endothelial cell proliferative effects of recombinant human erythropoietin would be useful in overcoming direct endothelium damage. More specifically, Carlini *et al.* do not teach a method of treating endothelial injury caused by mechanical damage, exposure to radiation, exposure to chemotherapeutic agents, inflammation, heart disease or cancer, in a subject, comprising administering an effective endothelial-protecting amount of erythropoietin to a subject in need of such treatment. It is only in view of the present invention does one arrive at the present invention directed to a method of treating endothelial injury as recited in amended claim 16.

Accordingly, Applicants respectfully submit that claim 16, and claim 21 that depends therefrom, is not anticipated under 35 U.S.C. § 102 in view of Carlini *et al.*, and request that this rejection be withdrawn.

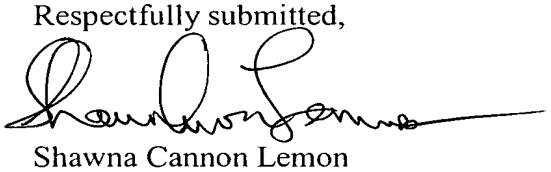
IV. Newly Added Claims

Applicants have added new claims 31-39. Support for new claims 30-39 can be found in the specification at page 12, line 6 through page 13, line 4, among other places. Applicants believe that no new matter is added by the addition of the new claims presented herein and respectfully request their entry into the present application.

V. Conclusion

In view of the foregoing remarks, Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. Any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,



Shawna Cannon Lemon
Registration No. 53,888

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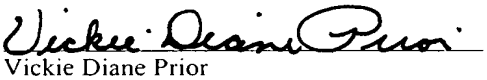

Vickie Diane Prior

Version With Markings To Show Changes Made

In the claims:

Please amend the claims as follows.

16. (Amended) A method of treating endothelial injury caused by mechanical damage, exposure to radiation, exposure to chemotherapeutic agents, inflammation, heart disease or cancer**[,]** in a subject **[in need of such treatment]**, comprising administering an effective endothelial-protecting amount of erythropoietin to said subject in need of such treatment.